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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,250	09/08/2003	Dana M. Fowlkes	FOWLKES=4D	1677

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EXAMINER
WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,250	FOWLKES ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-146* is/are pending in the application.

4a) Of the above claim(s) *7-30,32,46-49,51-113,124-127,132-134 and 137* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,31,33-45,50,114-123,128-131,135 and 136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-138 in the reply filed on 12/8/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' election of the species is noted and as follows:

A). Peptides of 10 amino acid residues as shown in the Table bridging pages 75-76. (Note this table recites a peptide i.e., X10C).

B). A structured Panel as of the peptides as elected under A.

C). Linear Cys as recited in A above.

D). Method by biological means

E). Target as human cytomegalovirus.

F). First member ligand as in A). above with the species as EHVCSWGWGRC.

G). Second library is benzodiazepines. (Note since the second library is specifically elected as the benzodiazepines hence, the election of the molecular weight of 300 for the chlorodiazepoxide is an unnecessary election).

Applicants submit that the claims that read on the elected species are claims 1-31, 33-45, 50-53, 58-120, 128-130, 135-138. However, the claims that read on the elected species are set as forth in Status of the claims below.

Status of Claims

Claims 1-146 are pending in the application.

Claims 7-30, 32, 46-49, 51-113, 124-127, 132-134, 137 and 139-146 are withdrawn from consideration as being drawn to the non-elected inventions and species. [Note claim 7, which reads on the peptides of the form (Xaa)m-R1-X(aa)n is outside the elected species of e.g., X10C. Likewise some of the panels contain two constants for which the X10C has only one constant i.e., cys (C). Also, claim 51 and the other claims read on different target protein than the elected CMV].

Claims 1-6, 31, 33-45, 50, 114-123, 128-131, 135-136 and 138 are under examination.

Specification

The lengthy (139 pages) specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

A). Claim 1 "they are not more than 41 amino acids long".

B). Claim 6 step of "in step (a) screening a structured panel of biased combinatorial peptide libraries, each library having one and only one constant residues.."

C). Claim 31 "m is greater than or equal to 5".

D). The whole of claim 37, claim 39, 42 and 43 and claim 136.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 31, 33-45, 50, 114-123, 128-131, 135-136 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for steroid family, specifically, estrogen as the nuclear receptor (i.e., target protein) and phage display library does not reasonably provide

enablement for a target protein, first and second libraries and any kind of expression system for said libraries. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the kind of ligand that can mediate a biological activity of a target protein. The type of biological activity of a target since binding can occur for any kind of target and ligand. It does not describe the kind and length of the primary and secondary combinatorial library.

2). The specification failed to provide working examples for any of the numerous and different type of identifying techniques that can be used in the instant method.

3). The breadth of the claims encompasses a large diversity of two types of library of peptides/protein. It is well known in the art, that it is often difficult whether the peptides in a library are equally represented in an expression system. The diversity of the inserts is not easily estimated. It may be for example, that only a small subset of possible peptide sequences are presented efficiently by a particular expression system. And, it is not always easy to follow the expression of peptides in particular cells; for example, to know whether or not a specific cell is expressing a member of the insert, especially for biological methods. Also, there are difficulties of enriching positive clones from phage libraries. Enrichment procedures are based on selective binding and elution onto a solid surface such as an immobilized receptor. Unfortunately, avidity effects arise due to multivalent binding of the phage and the general tendency of phage to contain two or more copies of the displayed polypeptide. The binding to the receptor surface therefore does not depend solely on the strength of interaction between the receptor and the displayed polypeptide. This causes difficulties in the identification of clones with

high affinity for the receptor; thus, there remain distinct deficiencies in the methods used to isolate and screen polypeptides, particularly antibodies, even in view of the development of phage libraries. Georgiou (USA 5,866,344 at col. 2, lines 1-23).

4). The state of the prior art is such that techniques are specifically applied for a predetermined target or core structure of a given peptide in a library. The instant specification at page 5, lines 14-20 disclose peptide libraries with specific component contained therein. The nonbiological synthesis of the library is disclosed at page 36, line 27 to page 38, line 27. It shows that the peptide library can be prepared by stepwise addition of **amino acids** i.e., the component amino acids of the library has to be known or characterized before synthesis can be consummated. Assuming one can make a library containing all or every possible compound combinations, the greatest challenge still faced by a skilled in this art is the screening of the library.

5). The art is inherently unpredictable because it is not possible to predict which predetermined amino acid species or peptide library would result in the desired binding ligand or inhibitory ligand with a desired pharmacologic activity. It is generally known that the conformational freedom that promotes

binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and which sites in a particular protein are best suited to insertion of multiple independent sequences. The complex spatial configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds). Chang et al (Molecular and Cellular Biology,1999) discloses that sequences flanking the core motif, LXXLL play a role in determining receptor selectivity. Chang discloses that not all LXXLL motifs are the same and that receptor binding selectivity can be achieved by altering sequences flanking the LXXLL core motif. Most notable was the discovery of a peptide which, when overexpressed in cells, selectively disrupted

ER.beta.- but not ER.alpha.-mediated reporter gene expression. Chang concludes that using a combinatorial approach to define cofactor-receptor interactions, demonstrates that not all LXXLL motifs are functionally equivalent.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous undefined claimed variables would produce the desired inhibitory ligand. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide a written description for the claimed structured panel of library and a peptide wherein the constant residue is "***within*** the middle 50%" of the sequence. The disclosure does not describe how a structured

panel can be made from a plurality of libraries, how the plurality of library form or structured into a panel or the minimum or maximum limit of the plurality contained in any one of the panel and a constant residue that is within 50% of the sequence. It is worthy to note, applicants' disclosure at e.g., page 28, which describes such in theory.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not teach how to screen a structured panel. The specification provides an unclear definition for said

structured panel. Not a single panel however has been made or exemplified such that a first combinatorial library is screened. The specification is replete with general statements as to what constitutes a panel. It does not describe how the different libraries have been made to a structured panel. This is made more complex as the examples in the specification provides for nothing more than prophetic statements for a library. There is no mention of a method of making and using a panel except for the prophetic statements made for the library.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 31, 33-45, 50, 114-123, 128-131 and 135-136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is unclear in the recitation at step © of "when the ligands are peptides". It is not clear as to which ligands are being referred to.

2. Claim 6 is confusing and does not seem to have nexus with claim 1, from which claim 5 depends. Does the first combinatorial library result from the screening of a structured panel of biased combinatorial library? The term "structured panel" is vague and not an art recognized term. The definition of the term in page 10, "panel…….there is some ***structural relationship*** between the member libraries…" But it is not clear how they are structurally related, since the length of the sequence is not shown, and which would be middle residue on library may not be middle residue of another library (since the length of the peptide libraries is not constant). Thus, it is not clear what does applicants mean by the terms "structured library" or "fixed position". This claim appears to broaden the base claim. While applicants can be their own lexicographers, however, it is expected that applicants would use term consistent with the prior art. Furthermore, it is not clear as to the basis or determination of "within the middle 50% of the peptide". The terms "predetermined" (claim 6); "suitable" (claim 36) are relative terms, which render the claims indefinite. Said terms are not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

3. Claim 136 is unclear as in what aspect a combinatorial library is classed as "simple".

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1 and 6 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 57, for example. of copending Application No. 09/050,359 ('359 application).

The instant claimed structured panel is the same as the structured panel of the '359 application except, worded differently. Furthermore, the formula recited in the '359 application, claim 47, would be inherent to the same instant claimed structured panel.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 31, 33-45, 50, 114-123, 128-131 and 135-136 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,617,114 ('114). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed method encompasses the method of the

'114 Patent. The '114 Patent recites only the specific amino acid core sequence obtained from the library.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5, 44 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Coughlin et al (U.S. 5,892,014).

Coughlin discloses at col.6, lines 7-31 a method of identifying a ligand which mediate the interaction between a target and its ligand partner comprising a) contacting a

candidate antagonist compound with a first compound which includes a recombinant PAR3(or agonist-binding fragment) on the one hand and with a second compound which includes thrombin or a PAR3 agonist on the other hand; b) determining whether the first and second compounds interact or are prevented from interaction by the candidate compound; and c) identifying antagonistic compounds as those which interfere with the interaction of the first compound(PAR3 receptor, target protein as claimed) to the second compound (PAR3 agonist, binding partner) and which thereby substantially reduce thrombin or PAR3 agonist-activated biological events. See further the Examples at col. 7 up to col. 15, line 35.

Claims 1-6 and 34-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Pinilla et al (USP 5,556,762).

Pinilla discloses at col. 34, line1 up to col.39, line 40 the same method as that claimed. See also claim 13 of Pinilla.

The library species, library of linear X10 Cys, target hCMV and benzodiazepine are free of prior art.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D.

Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
March 3, 2006